myopathy with deficiency of iron-sulfur cluster assembly enzyme

Myopathy with deficiency of iron-sulfur cluster assembly enzyme is an inherited disorder that primarily affects muscles used for movement (skeletal muscles). This condition does not usually affect other types of muscle, such as the heart (cardiac) muscle.

From early childhood, affected individuals experience extreme fatigue in response to physical activity (exercise intolerance). Mild exertion results in a rapid heartbeat (tachycardia), shortness of breath, and muscle weakness and pain. However, people with this condition typically have normal muscle strength when they are at rest.

Prolonged or recurrent physical activity causes more severe signs and symptoms, including a breakdown of muscle tissue (rhabdomyolysis). The destruction of muscle tissue releases a protein called myoglobin, which is processed by the kidneys and released in the urine (myoglobinuria). Myoglobin causes the urine to be red or brown. This protein can also damage the kidneys, in some cases leading to life-threatening kidney failure.

In most affected individuals, the muscle problems associated with this condition do not worsen with time. However, at least two people with a severe variant of this disorder have experienced progressive muscle weakness and wasting starting in childhood.

Frequency

This condition has been reported in several families of northern Swedish ancestry.

Genetic Changes

Myopathy with deficiency of iron-sulfur cluster assembly enzyme is caused by mutations in the *ISCU* gene. This gene provides instructions for making a protein called the iron-sulfur cluster assembly enzyme. As its name suggests, this enzyme is involved in the formation of clusters of iron and sulfur atoms (Fe-S clusters). These clusters are critical for the function of many different proteins, including those needed for DNA repair and the regulation of iron levels. Proteins containing Fe-S clusters are also necessary for energy production within mitochondria, which are the cell structures that convert the energy from food into a form that cells can use.

Mutations in the *ISCU* gene severely limit the amount of iron-sulfur cluster assembly enzyme that is made in cells. A shortage of this enzyme prevents the normal production of proteins that contain Fe-S clusters, which disrupts a variety of cellular activities. A reduction in the amount of iron-sulfur cluster assembly enzyme is particularly damaging to skeletal muscle cells. Within the mitochondria of these cells, a lack of this enzyme

causes problems with energy production and an overload of iron. These defects lead to exercise intolerance and the other features of myopathy with deficiency of iron-sulfur cluster assembly enzyme.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- hereditary myopathy with lactic acidosis
- HML
- iron-sulfur cluster deficiency myopathy
- myoglobinuria due to abnormal glycolysis
- myopathy with deficiency of ISCU
- myopathy with deficiency of succinate dehydrogenase and aconitase
- myopathy with exercise intolerance, Swedish type

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Myopathy with lactic acidosis, hereditary
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1850718/

Other Diagnosis and Management Resources

- GeneReview: Myopathy with Deficiency of ISCU
  https://www.ncbi.nlm.nih.gov/books/NBK5299
- MedlinePlus Encyclopedia: Rhabdomyolysis
  https://medlineplus.gov/ency/article/000473.htm

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html

- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Rhabdomyolysis
  https://medlineplus.gov/ency/article/000473.htm
- Health Topic: Muscle Disorders
  https://medlineplus.gov/muscledisorders.html

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Mitochondrial Myopathies Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Mitochondrial-myopathy-Information-Page

Educational Resources

- MalaCards: myopathy with deficiency of iron-sulfur cluster assembly enzyme
  http://www.malacards.org/card/myopathy_with_deficiency_of_iron_sulfur_cluster_assembly_enzyme
- Neuromuscular Disease Center, Washington University, St. Louis
  http://neuromuscular.wustl.edu/mitosyn.html#armmyop
- Orphanet: Hereditary myopathy with lactic acidosis due to ISCU deficiency
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=43115

Patient Support and Advocacy Resources

- Muscular Dystrophy Association: Facts About Mitochondrial Myopathies
  https://www.mda.org/sites/default/files/publications/Facts_MITO_P-216.pdf
- Resource list from the University of Kansas Medical Center: Muscular Dystrophy / Atrophy
  http://www.kumc.edu/gec/support/muscular.html
- United Mitochondrial Disease Foundation
  http://www.umdf.org/

GeneReviews

- Myopathy with Deficiency of ISCU
  https://www.ncbi.nlm.nih.gov/books/NBK5299

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28myopathy+%5Btiab%5D+AND+iron-sulfur+cluster+assembly+%5Btiab%5D%29+OR+%28iron-sulfur+cluster+%5Btiab%5D+AND+myopathy+%5Btiab%5D%29+OR+%28myopathy+%5Btiab%5D+AND+iscu+%5Btiab%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1440+days%22%5Bdp%5D

OMIM

- MYOPATHY WITH LACTIC ACIDOSIS, HEREDITARY
  http://omim.org/entry/255125

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